Repligen MAVEN

on-line Glucose and Lactate analysis

Integration with Getinge controllers

2025

GETINGE

Getinge and Repligen

On-Line Glucose and Lactate monitoring

MAVEN

REPLIGEN

GETINGE

Getinge MAVEN

Cutting edge technologies to drive process insights

- **Online monitoring**

Customers benefit from the integration of cutting-edge bioreactor systems and bes in class online glucose and lactate measurement technology, even on weekends!

- **Seamless integration**

Effortlessly incorporate MAVEN technology with Getinge bioreactors, providing deeper insights into your bioprocess for more insights and faster process optimization

- **Save time**

Easily enhance new or existing bioreactor systems with the plug and play addition of MAVEN with Livit Links, and intuitive Livit software for operation

- **Streamlined Automation**

Integrate MAVEN data into Livit Flex software and SCADA solutions, thereby optimizing process automation, workflows and directly resulting in valuable time savings during R&D

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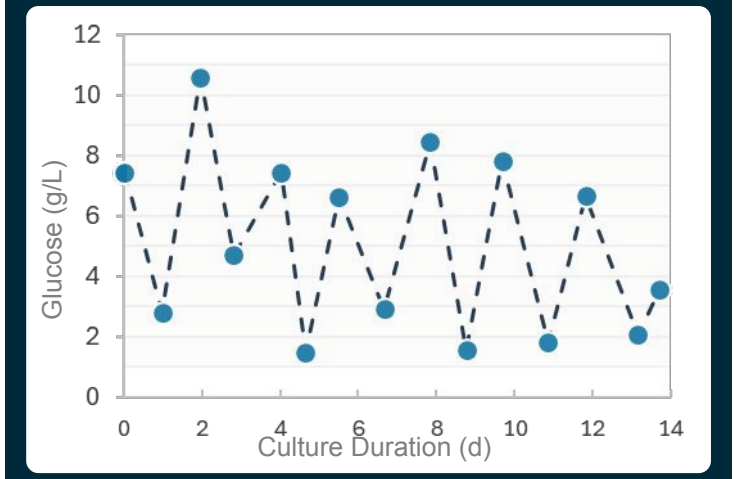
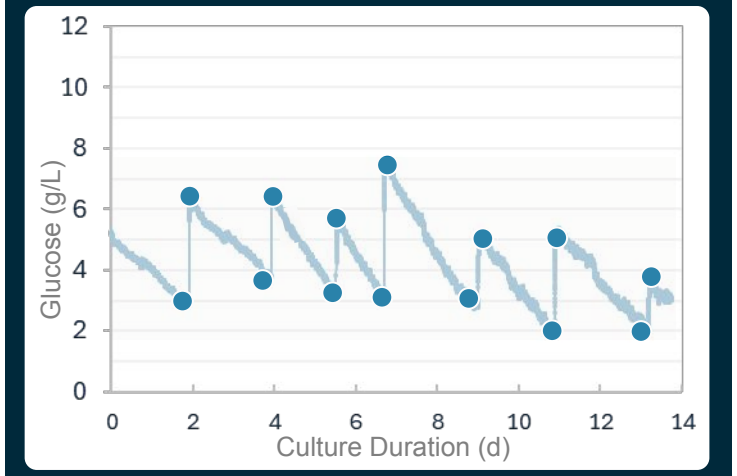
Improve Performance and Quality with PAT-based Feed Control

Off-line Monitoring with Manual Bolus Feeding



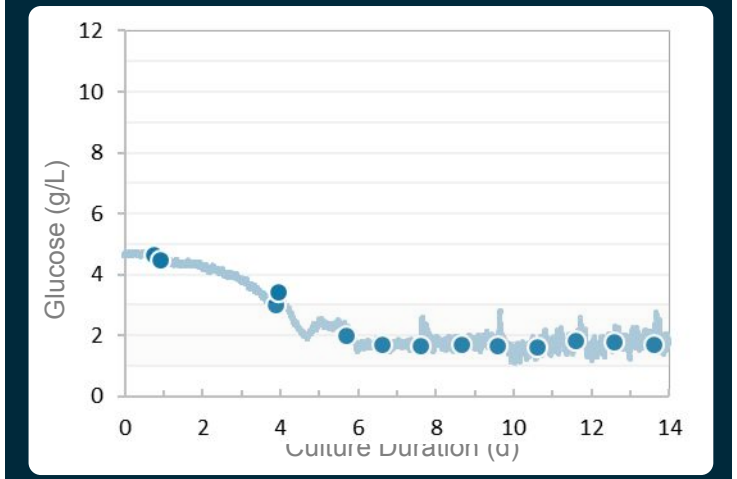
- Large nutrients fluctuations
- Accumulation of toxic metabolites
- Suboptimal product quality

Real-time Monitoring with Automatic Bolus Feeding



- Reduced nutrients fluctuations
- Faster response to culture conditions
- Improved growth profile

Real-time Monitoring with Automatic Continuous Feeding



- Improved process robustness
- Higher product titer
- Improved product quality

Importance of Glucose & Lactate Impact is Well Documented

pH-controlled delivery of glucose reduces lactate accumulation and increases titer


BIOTECHNOLOGY and BIOENGINEERING

Article

High-End pH-controlled delivery of glucose effectively suppresses lactate accumulation in CHO Fed-batch cultures

Matthew Gagnon, Gregory Hiller, Yen-Tung Luan, Amy Kittredge, Jordy DeFelice, Denis Drapeau

First published: 15 February 2011 | https://doi.org/10.1002/bit.23072 | Citations: 113

Low glucose intake can improve antitumor activity


JCI The Journal of Clinical Investigation

Inhibiting glycolytic metabolism enhances CD8+ T cell memory and antitumor function

Madhusudhanan Sukumar, ... , Nicholas P. Restifo, Luca Gattinoni

J Clin Invest. 2013;123(10):4479-4488. https://doi.org/10.1172/JCI69589.

Glucose feed control affects mAb glycosylation profile and titer

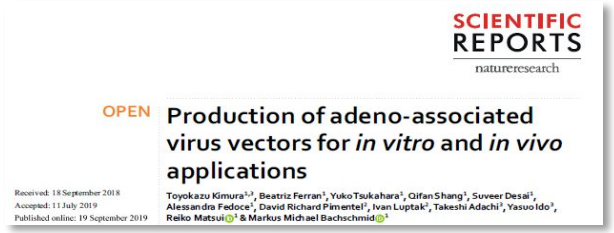

ARTICLE

BIOTECHNOLOGY and BIOENGINEERING

Amino Acid and Glucose Metabolism in Fed-Batch CHO Cell Culture Affects Antibody Production and Glycosylation

Yuzhou Fan,[1,2] Ioscani Jimenez Del Val,[3] Christian Müller,[2] Jette Wagtberg Sen,[2] Søren Kofoed Rasmussen,[2] Cleo Kontoravdi,[3] Dietmar Weilguny,[2] Mikael Rørdam Andersen[1]

Controlled glucose supplementation shown to increase viral vector titer 3-4x


SCIENTIFIC REPORTS

nature research

OPEN

Production of adeno-associated virus vectors for *in vitro* and *in vivo* applications

Received: 18 September 2018
Accepted: 11 July 2019
Published online: 19 September 2019

Toyokazu Kimura[1,2], Beatriz Ferran[1], Yuko Tsukahara[1], Qifan Shang[1], Suveer Desai[1], Alessandra Fedoce[1], David Richard Pimentel[1], Ivan Luptak[1], Takeshi Adachi[1], Yasuo Ido[3], Reiko Matsui[1] & Markus Michael Bachschmid[1]

1. Gagnon et. al, High-end pH-controlled delivery of glucose effectively suppresses lactate accumulation in CHO fed-batch cultures. Biotechnol Bioeng. 2011 Jun;108(6):1328-37. doi: 10.1002/bit.23072. Epub 2011 Feb 24.
2. Sukumar et. al., Inhibiting glycolytic metabolism enhances CD8+ T cell memory and antitumor function. J Clin Invest. 2013 Oct;123(10):4479-88. doi: 10.1172/JCI69589. Epub 2013 Sep 16. PMID: 24091329; PMCID: PMC3784544
3. Fan et al, Amino acid and glucose metabolism in fed-batch CHO cell culture affects antibody production and glycosylation. Biotechnol Bioeng. 2015 Mar;112(3):521-35. doi: 10.1002/bit.25458. Epub 2014 Oct 10.
4. Kimura, T., Ferran, B., Tsukahara, Y. et al. Production of adeno-associated virus vectors for in vitro and in vivo applications. Sci Rep 9, 13601 (2019). https://doi.org/10.1038/s41598-019-49824-w

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Summary

Plug in. Monitor. Optimize.

- Increase process insights with Glucose and Lactate through the MAVEN integrated with the Livit Flex
- Plug and play integration, allowing precise process control through SCADA software
- Faster process optimization, higher yield
- Automation reduces the need for operator involvement, thereby freeing up time for other tasks

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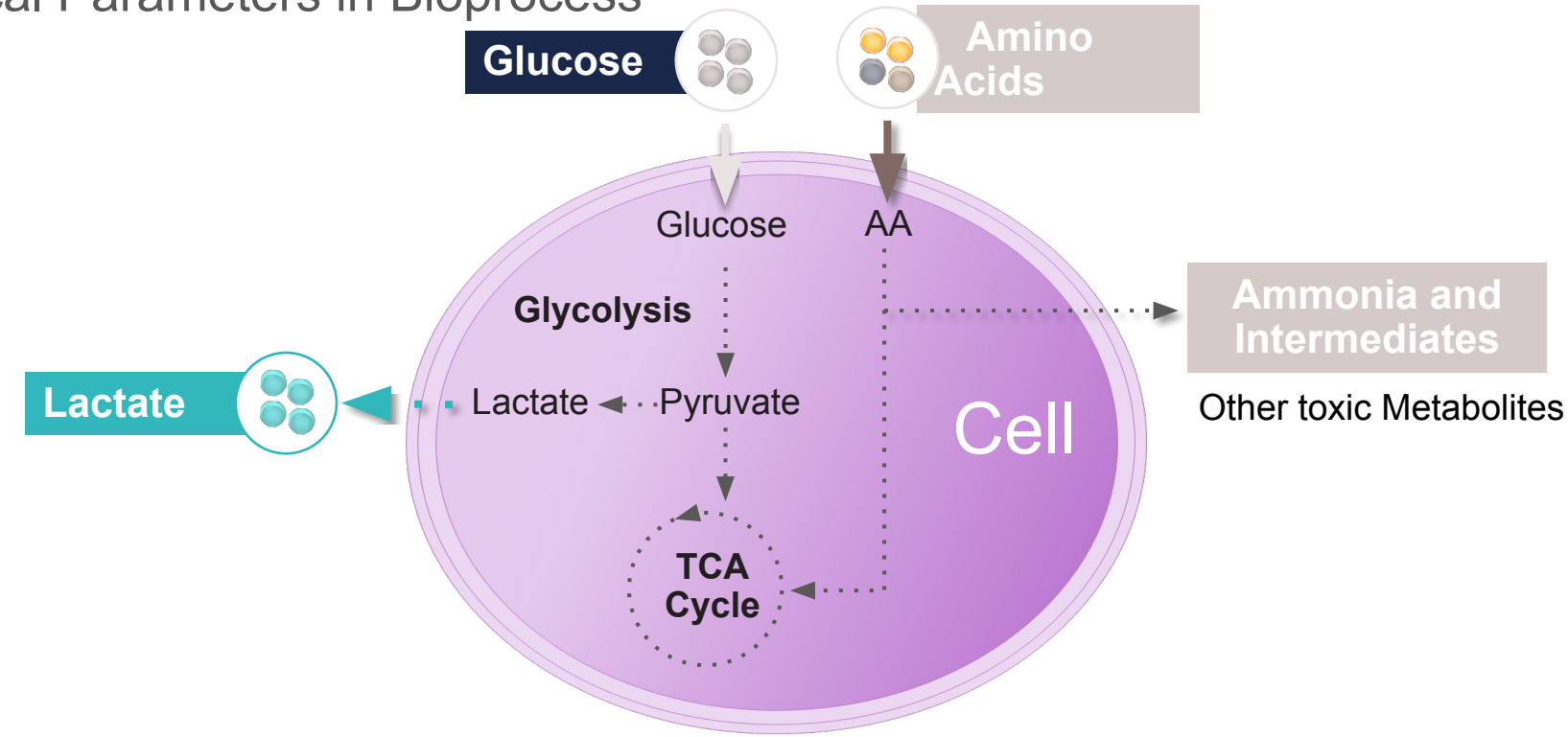
PASSION FOR LIFE

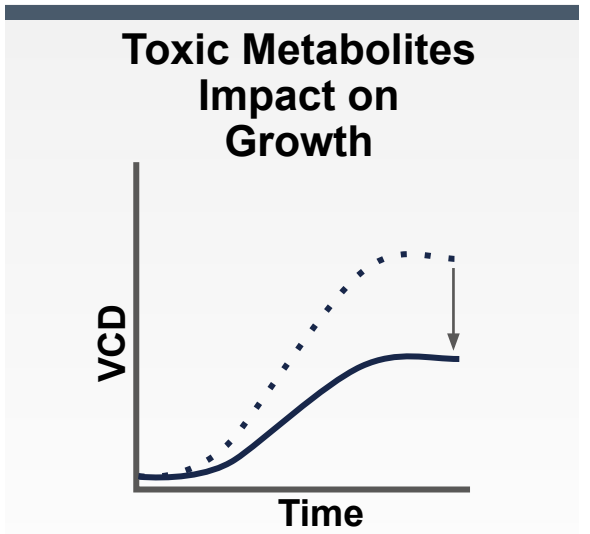
Appendix

Additional material

Glucose and Lactate

Critical Parameters in Bioprocess





Glucose and Lactate Need to be Closely Controlled Throughout the Process for Optimal Productivity and Consistent Product Quality

ereira, S., (2018),. *Biotechnol*. J., 13: 1700499. https://doi.org/10.1002/biot.201700499

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Interface Options for MAVEN

Reusable Diffusion Probes

Available volumes:

- 2, 3 or 5 L reactors – 232 mm
- 7 L reactors – 332 mm
- 15 L reactors – 432 mm

Single-Use Diffusion Probes

Custom AppliFlex enables benefits of the Maven system in single-use bioreactors

Available volumes:

- 3 L AppliFlex ST RnD

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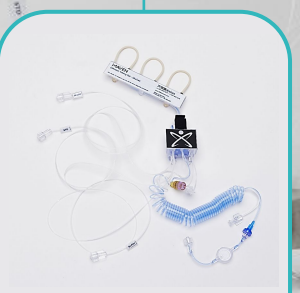
Components

Buffer Solution

Calibration Standard

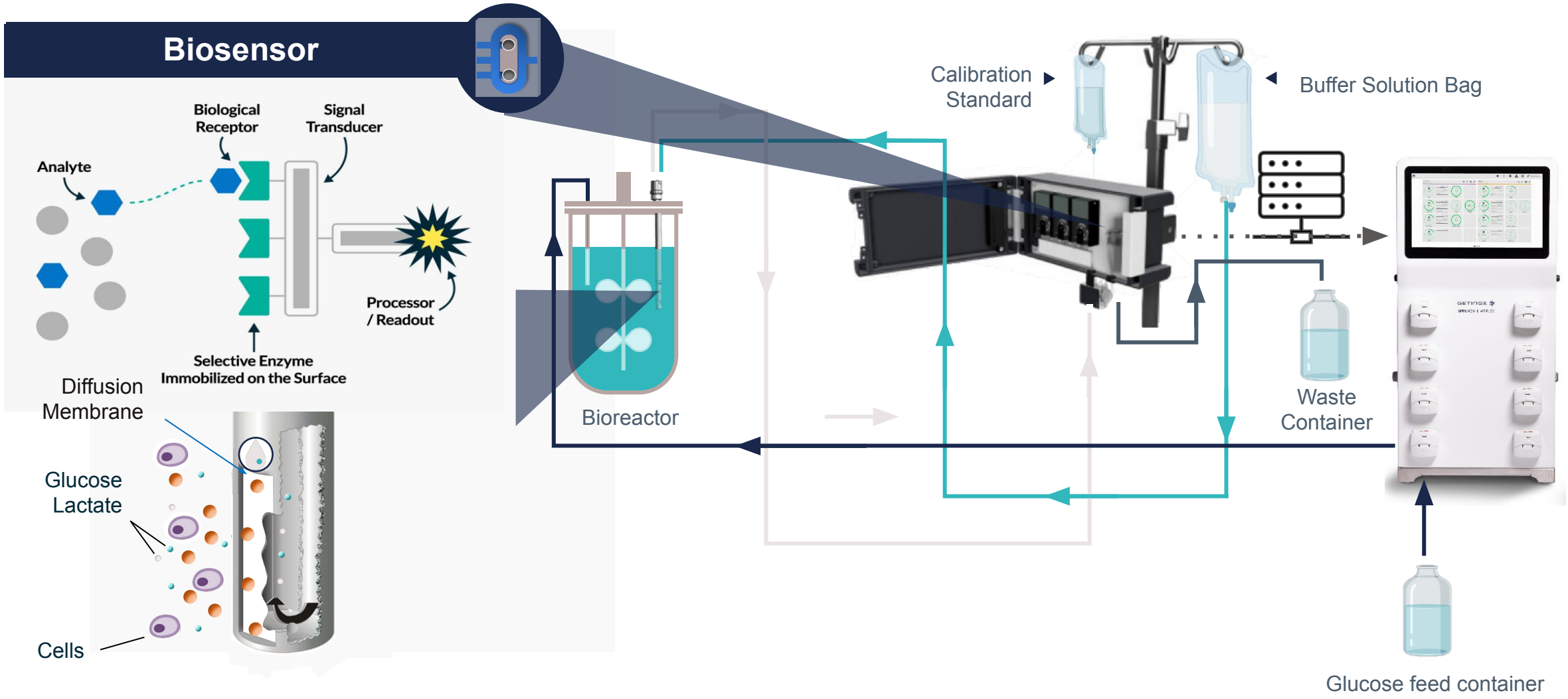


Tubing Set

Sensor

Diffusion Probes

How Does the MAVEN Work?



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The Goldilocks

GLUCOSE CONCENTRATION &FEEDING

TOO LOW

- **Inhibit** cell growth
- **Reduced** productivity
- **Increased** production of ammonia

TOO HIGH

- **Favors** growth over CQAs
- **Increases** accumulation of lactate & osmolality
- **High** glycation and **incorrect** glycosylation

AMINO ACIDS IN BASAL & FEED MEDIA

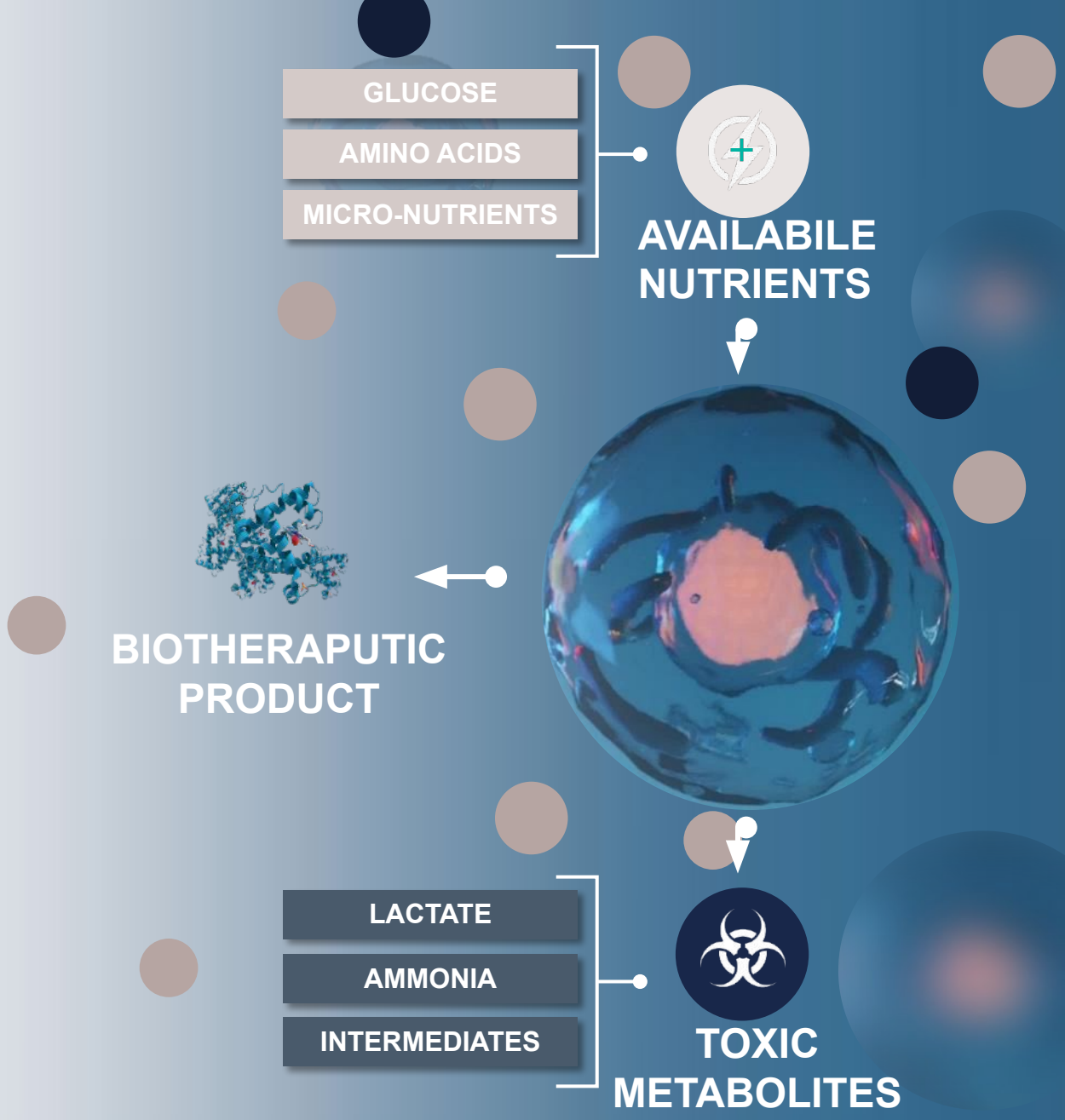
TOO LOW

- **Starve** protein production
- Can lead to **corrupt** protein sequence

TOO HIGH

- Produce **wrong protein charge variants**
- **Favor** growth over protein production

*A small **difference in the timing** of glucose feeding may cause cultures with very similar metabolic behavior to **diverge to different outcomes**"*



Pereira et al., *Biotechnol*. J. 2018, 13, 1700499; Dickson, *Curr. Opin. Biotechnol*. 2014, 30, 73

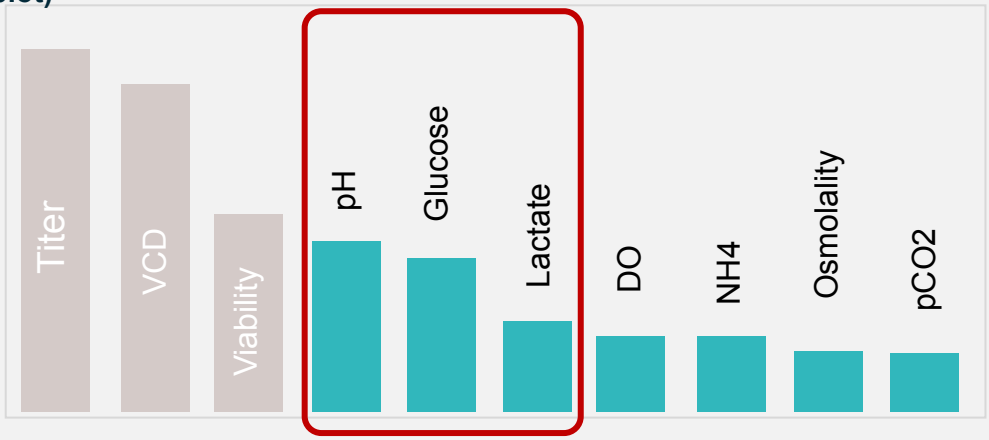
You already measure glucose daily…

Why measure it continuously?

- Based on data published by AMGEN, Glucose and Lactate have the highest impact on cell culture parameters: VCD, Titer and Viability
- Modulating Glucose enables management of Lactate, Ammonia, and Osmolality which are key to controlling CQAs
- Continuous glucose control leads to optimal cell culture conditions and CQAs

Fan Y, et al. Biotechnol Bioeng. 2015 Mar;112(3):521-35.

Relative Affect of Process Parameters on Process Performance (VIP plot)[1]



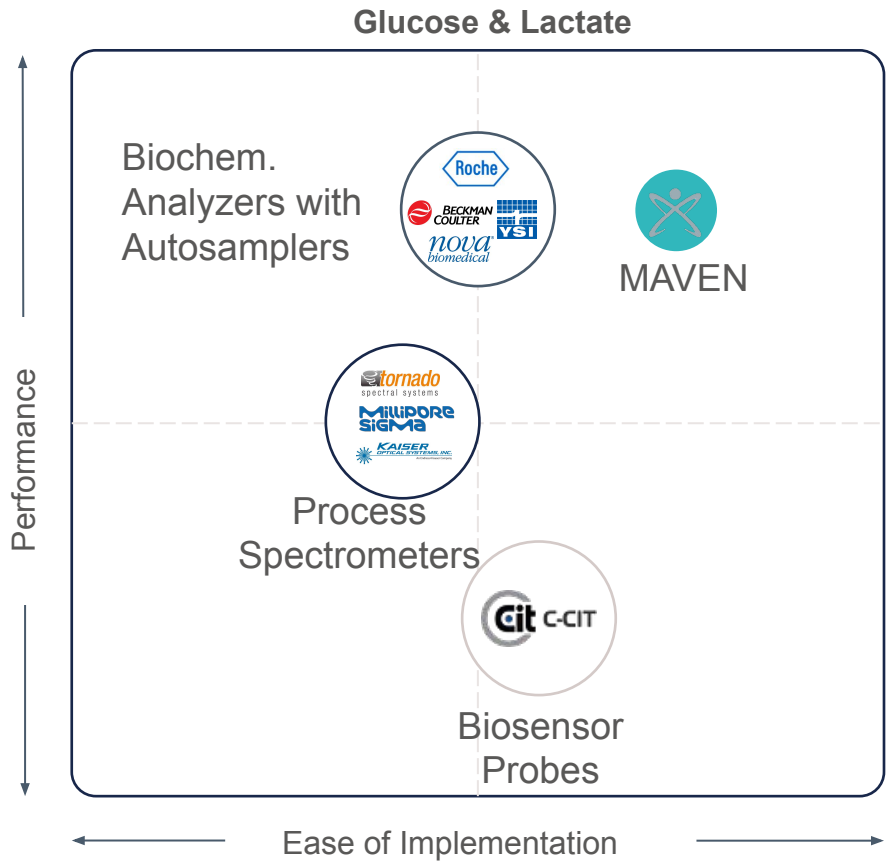
Anurag S. Rathore. BioPharm International, 2007 BioPharm International-10-01-2007, Volume 20, Issue 10 Pages: 40–45

"Unbalanced nutrients (glucose, amino acids, etc.) lead to accumulation of ammonia and lactate inhibiting cell growth"

Mulukutla B.C., Kale J., Kalomeris T., Jacobs M., Hiller G.W.. Biotechnol. Bioeng. 2017;114:1779–1790.

Because your cells need just enough glucose, not more, not less

Competitive Positioning



	On-Line Biochem. Analyzes	Process Spectrometers	Biosensor Probes	MAVEN
Technology	Biosensor Photometry	Raman NIR	Biosensor	Biosensor
Sample Loss	Yes	No	No	No
Analytes	Many	Few	1 or 2	2
Robustness	++	++	+	++++
Ease of Use	+	++	++	+++
Contamination Risk	+++	+	+++	++
Process Control	+	+++	+	++++
Cost	$$$$	$$$$	$	$$

Maven is a safe and reliable method for continuous monitoring of Glucose-Lactate making it the easiest to implement PAT tool available

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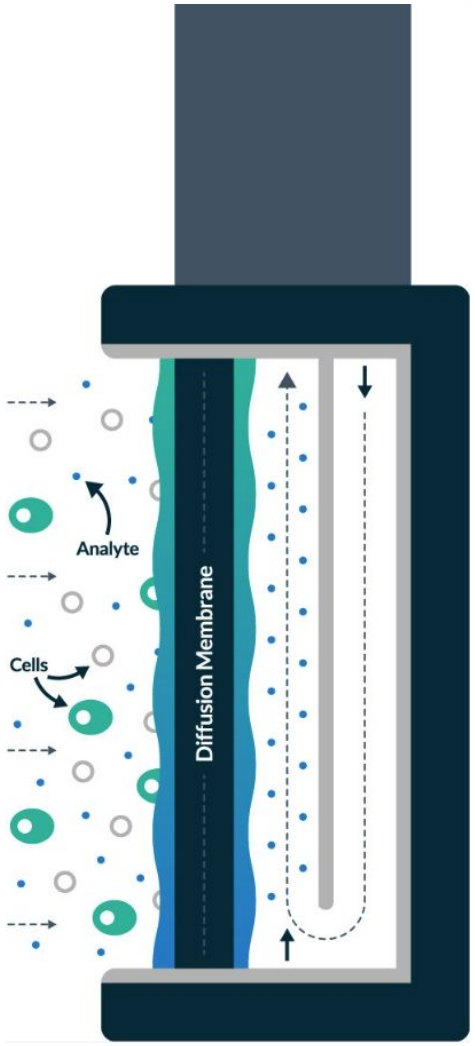
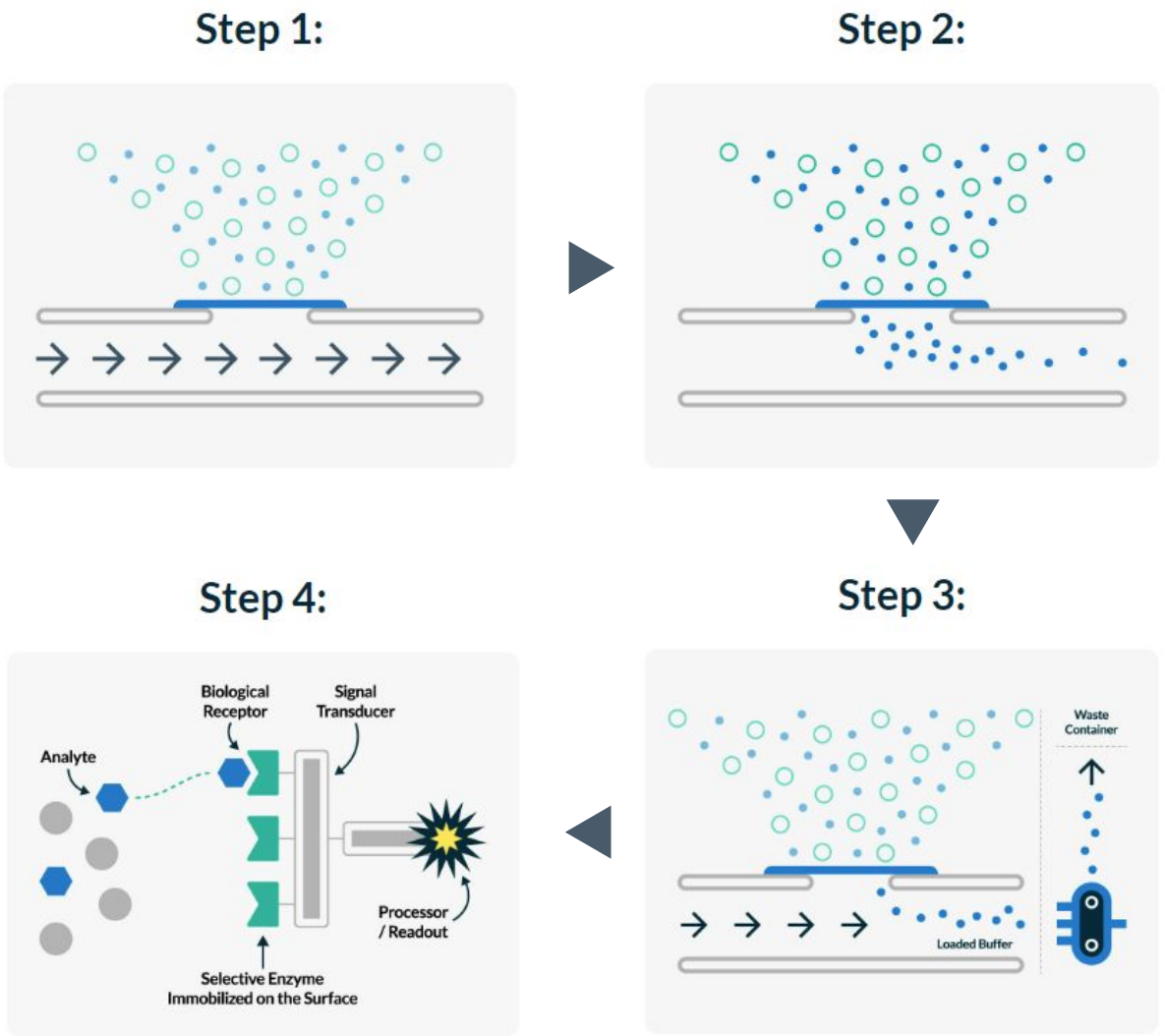
Precise & Sterile Measurement

Automatic, on-line glucose and lactate monitoring

- Diffusion probe installed in bioreactor connects to biosensor
- Enzyme-based biosensor detects glucose to 0.01g/L and lactate to 0.05g/L
- Glucose and lactate molecules diffuse through the semipermeable membrane into the buffer fluid
- No loss of bioreactor volume
- No increased risk of contamination
- Enables online analytics and process control





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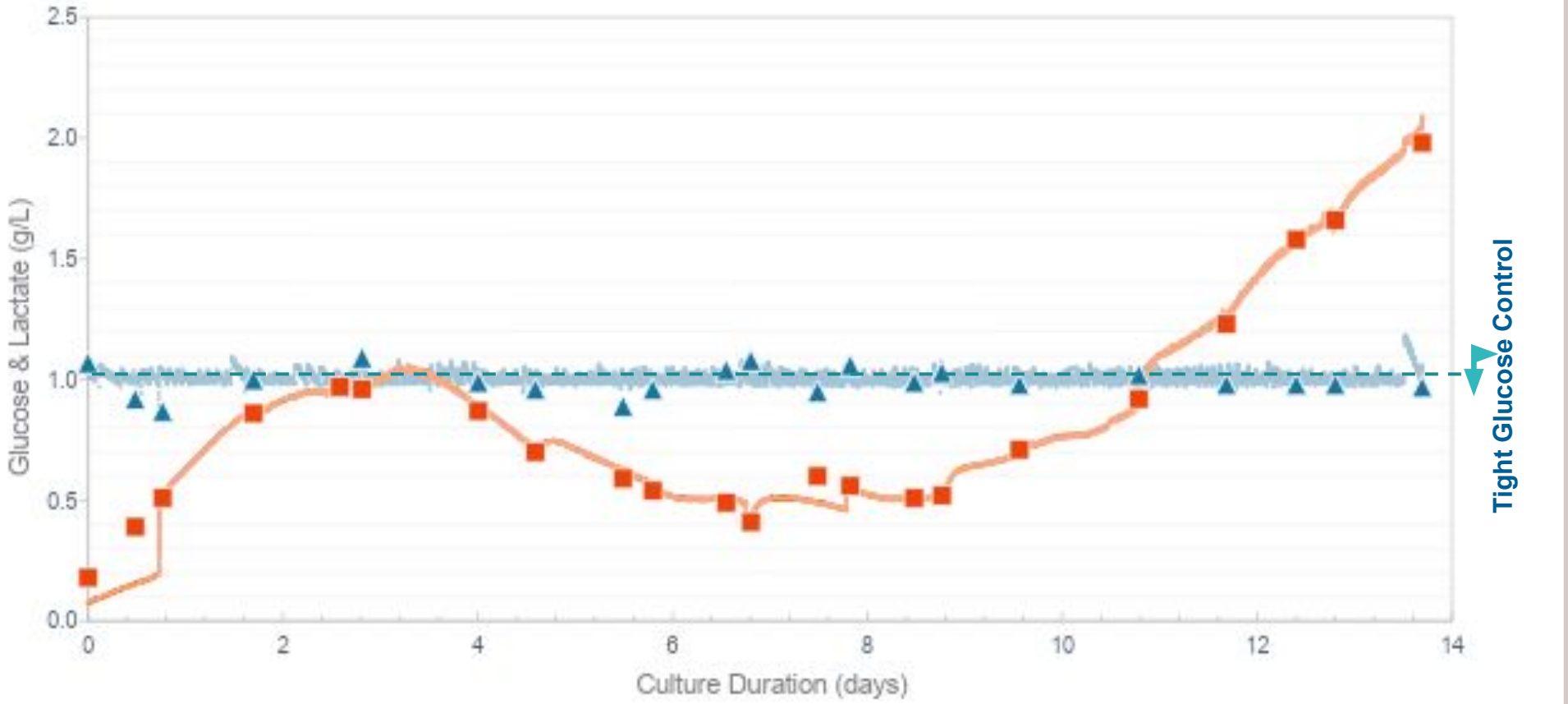
Appendix: On-Line Monitoring with Continuous Feeding

3L Bioreactor

- NISTCHO Cell Line
- ExCELL Advanced Media
- ExCELL Feed w/o Gluc.
- Gluc. Feed Continuous
- 2 min Measurement *f*
- 1 g/L Gluc. Setpoint

Legend

- MAVEN Glucose
- BioProfile FLEX2 Glucose
- MAVEN Lactate
- BioProfile FLEX2 Lactate



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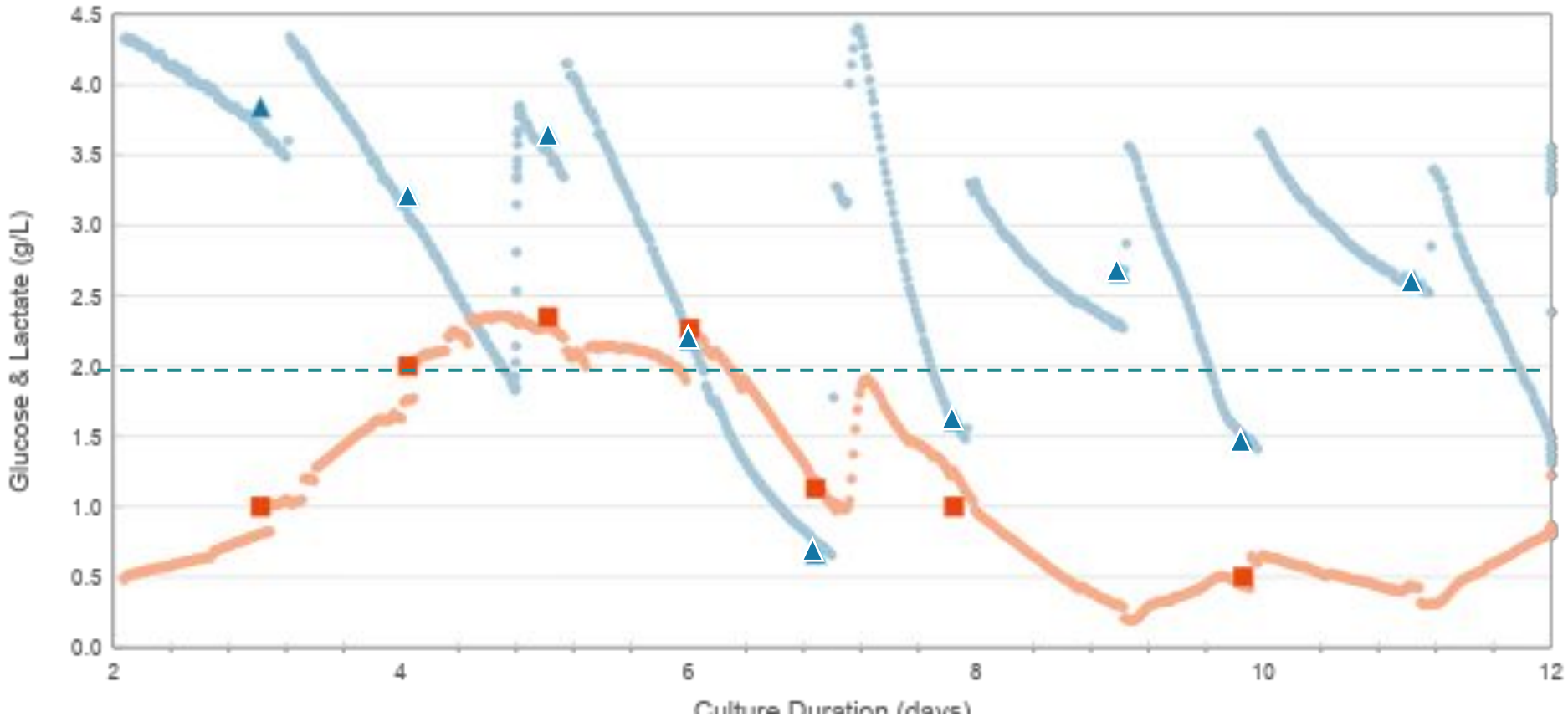
Appendix: On-Line Monitoring with Automatic Bolus Feeding

10L Bioreactor

- GS-CHO Cell Line
- CD FortiCHO Media
- EFC+ Feed with Gluc.
- 20 min measurement *f*
- 2 g/L Gluc. Feed Trigger

Legend

- MAVEN Glucose
- Cedex Glucose
- MAVEN Lactate
- Cedex Lactate



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Importance of Glucose & Lactate Impact is Well Documented

Media optimization for recombinant insulin production

Enhanced production of human mini-proinsulin in fed-batch cultures at high cell density of Escherichia coli BL21(DE3)[pET-3aT2M2]

C S Shin [1], M S Hong, C S Bae, J Lee

Control of by products by optimizing glucose concentrations during the process

Effect of glucose supply strategy on acetate accumulation, growth, and recombinant protein production by Escherichia coli BL21 (lambdaDE3) and Escherichia coli JM109

J Shiloach [1], J Kaufman, A S Guillard, R Fass

Glucose feed control to switch cells from growth to production phase

Strategies for efficient production of recombinant proteins in *Escherichia coli*: alleviating the host burden and enhancing protein activity

Zi-Xu Zhang, Fang-Tong Nong, Yu-Zhou Wang, Chun-Xiao Yan, Yang Gu, Ping Song & Xiao-Man Sun

Can track induction (both manual and auto-induction) when using lac operon

Recombinant protein expression in *Escherichia coli*: advances and challenges


Germán L. Rosano[1,2*]


Eduardo A. Ceccarelli[1,2]

[1] Instituto de Biología Molecular y Celular de Rosario, Consejo Nacional de Investigaciones Científicas y Técnicas, Rosario, Argentina
[2] Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Rosario, Argentina

Integration with Getinge controllers

Seamless connectivity

Livit Flex

- Livit Link for the MAVEN allows plug and play integration into the Livit control tower. Process values can be used to program control loops and schedule events with the combination of the Livit Software and SCADA software

my-Control and ez2-Control

- Connected as two analog inputs (for Glucose and Lactate). Process values can be used to program control loops or schedule events with SCADA software